Original Article

Distribution of iron status among urban Chinese women

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Background and Objectives: To assess the distribution of serum ferritin, serum soluble transferrin receptor and body iron among girls and women by age and anaemia. **Methods and Study Design:** Serum ferritin, serum soluble transferrin receptor and high sensitive C-reactive protein of 1625 and 1372 women in general and anaemic were measured in the National Health and Nutrition Survey commenced in 2010. **Results:** The distributions of serum ferritin, serum soluble transferrin receptor and body iron for 6-11-y, 12-17-y, 18-44-y, 45-59-y and ≥60-y subgroups were significantly different. Both in population-representative women and those anaemic, the iron status of 18-44-y women was the lowest and that of 12-17-y girls the second lowest. The iron status of anaemic women was lower than that in representative women at ages 12-17 y, 18-44 y, 45-59 y and ≥60 y. **Conclusion:** Iron status in women of different ages and anaemic had different distributions, but consistently lower than that of population-representative women. The observed iron status of Chinese urban women supports program planning for iron nutrition promotion in women. Iron status information is also needed for men and to understand the pathogenesis which may be related to intake or loss.

Key Words: iron deficiency, anaemia, serum ferritin, serum soluble transferrin receptor, body iron

INTRODUCTION

Iron deficiency (ID) is reported one of the most common nutrient deficiencies in the world and can develop iron deficiency anaemia known as the severe stage of ID. ID affects nearly 2 billion people worldwide, or about one third of the world's population.[1] Sufficient evidence has shown that ID results in fatigue, decreased work capacity and impaired immune function etc.[2-4] In addition, ID could lead to reduced cognitive and development in young children and the adverse effects may not recover completely through iron intervention.[5-6] Although national intervention projects on ID have been developed in the past decades in many countries and regions, the data for iron status of population are far less available than that required for understanding iron nutrition status of the population as well as needed for intervention for high risk population of ID such as childbearing aged women. This study, as a part of National Nutrition and Health Survey project, was purposely designed to observe iron status of Chinese girls and childbearing women through the measurement of parameters of iron and statistical analysis on both healthy and anaemic samples of the groups in order to accumulate necessary scientific data for improvement of iron nutrition status on the above mentioned population.

METHODS

Study population

Sampling of participants was based on a general large city population sampling frame for the 2010 China National Nutrition and Health Survey, which is a nationally representative cross-sectional survey covering all parts of mainland of China. A stratified multistage cluster sampling method was used for participants' selection based on the selection of cities, districts, counties, communities, households and individuals in families. All the cities, districts or counties were divided into four categories including big cities, medium and small cities, non-poverty rural, poverty rural based on the scale and the economic statistic data. Thirty-four provincial capitals and big industrial cities were sampled as big cities. Six resident committees were selected in each city by Probability Proportionate to Size Sampling. Seventy-five households were randomly selected in each resident community. All the members of the households were selected samples. Considering some limitations such as total available funds, resampling for measuring iron indicator was conducted based on the total samples. The participants were divided into the whole group that included both healthy and anaemic participants, and the anaemic group which only included anaemic participants. Anaemia was defined according to WHO crite-

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ria.[7] Eight subgroups of the whole group for male and female at ages of 6-17 y, 18-44 y, 45-59 y and ≥60 y. Eight subgroups of the anaemic group were divided by the sex and age as the same as for the whole group. Sample size was estimated using standard deviation-based calculations. The resampling was randomly taken from the original samples in each subgroup according to the age and sex with t=1.96, S=60 μg/L and d=5 μg/L in the whole group, and t=1.96, S=45 μg/L and d=5 μg/L in the anaemic group, respectively. If the calculated sample size was larger than the actual size of a subgroup, whole participants of the subgroup would be sampled. The ethic committee of Institute for Nutrition and Food Safety approved the projects with the file number of 2013-018. All the participants were fully informed and consent forms were signed and collected.

Non-pregnant females (≥6 y) were involved in the analysis of both women group (WG) and anaemic women group (AWG) in the present study. Maternal anaemia was defined according to the WHO threshold as haemoglobin <115 g/ L for children aged 6-11 y, <120 g/ L for women aged ≥12 y with haemoglobin values adjusted for altitude. Participants were excluded if the blood specimens were in the state of the hemolysis, clots, or rich in chylomicrons. The total numbers of specimens were 1800 women in WG and 1481 in AWG, respectively.

Laboratory analysis

The veinous blood was collected and divided into the anticoagulation tube and serum separator tube, respectively. The hemoglobin (Hb) was measured by cyanmethemoglobin method from the anticoagulation tube in the field survey. The blood samples in the serum separator tube were promptly centrifuged at 3000×g for 15 mins after blood collection, divided into aliquots of serum and frozen at -80℃ for subsequent assays: serum ferritin (SF), serum soluble transferrin receptor (sTfR) and high sensitive C-reactive protein (hsCRP). SF, sTfR and hsCRP were measured by the RocheTina-quant immunoturbidimetric assay on the Hitachi 7600-010 automatic biochemical analyzer (Roche Diagnostics).[8-10] The between-day CV was 5.6-5.9% for the SF assay, 1.7-2.5% for the sTfR assay and 1.1-1.7% for the hsCRP assay. The intra-day CV was 1.3-4.3% for the SF assay, 0.9-1.1% for the sTfR assay and 5.0-9.9% for the hsCRP assay.

Statistical analysis

We used SPSS 19 for statistical analyses. Statistical significance was defined as $p<0.05$. Body iron was calculated as previously described from sTfR and SF concentrations by using a formula from Cook et al[11]

Body iron (BI, mg/kg) =

-[log (sTfR * 1000/SF) -2.8229] / 0.1207

To convert the Roche sTfR concentration to that equivalent to the Flowers assay, we applied a conversion equation[12]:

Flowers sTfR = 1.5 * Roche sTfR + 0.35 mg/L

We log transformed SF [lg(SF)] and sTfR [lg(sTfR)] to normalize the distributions because SF and sTfR concentrations were positively skewed. SF and sTfR distributions were described as geometric means and 5th, 25th, 50th (median), 75th, and 95th percentiles by age subgroups in both WG and AWG. For the distributions of BI, arithmetic means and selected percentiles were used since BI was not skewed distributed. Differences in mean values among 5 age subgroups (6-11, 12-17, 18-44, 45-59 and ≥60-y-old) were analyzed by ANOVA test. In addition, the independent t-test analysis was conducted on the lg(SF), lg(sTfR) and BI of the samples between WG and AWG. Differences in mean values of Hb in the WG among 5 age subgroups were analyzed by ANOVA test. As Hb level in AWG was not normal distributed, non-parametric analysis was used for comparing the differences of Hb concentration among 5 age subgroups.

RESULTS

Sampled participants

WG consisted of 484 girls (6-17 y) and 1316 women (18 y and above). A total of 102 participants (15 girls and 87 women) who had abnormal levels of hsCRP and 73 pregnant women were excluded. Therefore, the present study of iron status in WG was performed on 469 girls and 1156 women. AWG consisted of 145 girls (6-17 y) and 1336 women (18 y and above). A total of 23 participants (1 girl and 22 women) who had abnormal levels of hsCRP were excluded, and 86 pregnant women were excluded. Therefore, the present study of iron status in AWG was performed on 144 girls and 1228 women. The average Hb concentrations ranged from 135 to 140 g/L in WG and from 107 to 110 g/L in AWG, which showed that the difference of two groups was significant ($p<0.01$). In WG, the Hb level of 18-44-y subgroup was significantly lower than those of 6-11 and 12-17-y subgroup ($p<0.01$), and Hb concentrations of 45-59 and ≥60-y subgroups were significantly lower than that of 12-17-y subgroup ($p<0.05$). In AWG, Hb concentration of 6-11-y subgroup was the lowest among all the subgroups ($p<0.05$). Hb concentration of ≥60-y subgroup was significantly higher than that of the 45-59-y subgroup ($p<0.05$). The basic information is shown in Table 1.

Iron status

Distribution data of SF, sTfR and BI concentrations for girls and women in the WG and AWG is listed in Table 2.

As shown in Table 2 and Figure 2 for WG, the SF concentrations from the 12-17 and 18-44-y subgroups were significantly lower than the other three subgroups ($p<0.01$). The SF concentration of 60-y subgroup was the

Table 1. Mean Hb concentrations (g/L) of girls and women in WG and AWG[†]

Age (y)	WG		AWG	
	n	Hb	n	Hb
6-11	238	139±12.2	43	107±9.8[††]
12-17	231	140±12.1	101	107±15.5[‡††]
18-44	409	135±14.7[‡§]	488	109±12.6[‡††]
45-59	384	137±16.9[§]	404	107±15.1[‡††]
≥60	363	137±15.2[§]	336	110±13.4[‡¶††]

[†]Mean Values are arithmetic means±SDs for Hb by different age subgroup in WG and AWG, respectively.

[‡]$p<0.05$ compared with 6-11-y subgroup; [§]$p<0.05$ compared with 12-17-y subgroup; [¶]$p<0.05$ compared with 45-59-y subgroup. [††]$p<0.01$ compared with WG in the same age subgroup.

Table 2. Mean, median and selected percentiles of SF (μg/L), sTfR (mg/L) and BI concentrations (mg/kg) of girls and women in WG and AWG[†]

	Age (y)	6-11		12-17		18-44		45-59		≥60	
	Group	WG	AWG	WG	AWG	WG	AWG	WG	AWG	WG	AWG
SF	Mean	70.5	61.9	50.1[‡]	25.2[‡§§]	48.5[‡]	23.7[‡§§]	98.6[‡§¶]	56.5[§¶§§]	152.2[‡§¶††]	122.1[‡§¶††§§]
		(66.1, 75.1)	(52.5, 72.9)	(45.1, 55.7)	(18.8, 33.8)	(44.1, 53.4)	(21.2, 26.6)	(89.7, 108.4)	(49.5, 64.5)	(140.8, 164.4)	(110.6, 134.9)
	5 percentile	32.8	29.2	14.1	2.6	9.4	3.9	14.4	6.5	44.4	18.1
	25 percentile	55.4	46.2	36.0	12.8	31.8	11.5	60.8	17.0	99.9	81.2
	Median	69.0	62.8	57.5	36.0	55.4	22.0	114.2	79.8	162.1	139.4
	75 percentile	96.8	89.4	84.5	66.8	87.8	60.4	187.9	158.0	255.6	235.8
	95 percentile	149.6	131.2	138.8	126.8	190.3	152.1	365.1	299.5	468.8	417.8
sTfR	Mean	3.30	3.08	3.13[‡‡]	4.17[‡§§]	3.06[‡]	4.20[‡§§]	3.01[‡]	4.03[‡§§]	3.00[‡]	3.26[§¶††§§]
		(3.21, 3.39)	(2.75, 3.44)	(3.02, 3.24)	(3.75, 4.64)	(2.96, 3.17)	(4.00, 4.42)	(2.92, 3.10)	(3.82, 4.26)	(2.92, 3.09)	(3.13, 3.41)
	5 percentile	2.47	1.39	2.16	2.04	1.97	1.99	1.98	2.00	2.02	2.06
	25 percentile	2.93	2.65	2.60	2.88	2.51	2.63	2.46	2.71	2.52	2.52
	Median	3.22	3.13	3.04	3.64	2.94	3.77	2.88	3.40	2.95	3.06
	75 percentile	3.60	3.72	3.50	5.30	3.45	6.12	3.48	5.90	3.46	3.84
	95 percentile	4.80	6.23	5.16	12.40	6.76	12.95	5.21	12.90	4.64	7.05
BI	Mean	7.84	7.60	6.79[‡]	3.33[‡§§]	6.73[‡]	3.08[‡§§]	9.35[‡§¶]	6.34[§¶§§]	10.92[‡§¶††]	9.84[§¶††‡‡§§]
		(7.57, 8.10)	(6.91, 8.28)	(6.35, 7.23)	(2.04, 4.61)	(6.31, 7.15)	(2.54, 3.62)	(8.96, 9.74)	(5.73, 6.95)	(10.60, 11.23)	(9.41, 10.28)
	5 percentile	4.30	5.30	1.02	-9.40	-1.71	-6.36	1.66	-4.73	5.91	0.13
	25 percentile	6.72	6.34	5.44	-0.24	5.10	-0.99	7.71	1.03	9.30	8.49
	Median	8.03	7.49	7.21	5.45	7.51	3.54	9.94	8.36	11.07	10.53
	75 percentile	9.11	9.09	9.06	7.68	9.40	7.92	11.87	11.08	12.85	12.42
	95 percentile	10.78	10.42	11.09	10.97	12.03	11.34	14.42	13.69	15.56	14.66

[†]Mean values are geometric means (95% CIs) for SF, sTfR and arithmetic means (95% CIs) for BI by different age subgroup in WG and AWG, respectively.
[‡]$p<0.01$ compared with 6-11-y subgroup; [§]$p<0.01$ compared with 12-17-y subgroup; [¶]$p<0.01$ compared with 18-44-y subgroup; [††]$p<0.01$compared with 45-59-y subgroup; [‡‡]$p<0.05$ compared with 6-11-y subgroup.
[§§]$p<0.01$ compared with WG in the same age subgroup.

highest (p<0.01). The SF concentration in the 45-59-y subgroup was significantly lower than that of ≥60-y subgroup (p<0.01), but these two subgroups were significantly higher than the other three subgroups (p<0.01).

As shown in Table 2 and Figure 4 for WG, the sTfR concentration in the 6-11-y subgroup was significantly greater compared with the other four subgroups (p< 0.05). There were no significant statistical differences among the other four subgroups.

As shown in Table 2 and Figure 6 for WG, The BI concentration among the 18-44-y subgroup was significantly lower than the other four subgroups (p<0.01). The BI concentration in the 45-59-y subgroup was significantly lower than ≥60-y subgroup (p<0.01). The BI concentrations in both the 45-59 and ≥60-y subgroups were significantly greater than the other three subgroups (p< 0.01), in comparison to that there was no difference between the 12-17 and 18-44-y subgroups.

As shown in Table 2 and Figure 2 for AWG, the SF concentration in the ≥60-y subgroup was the highest (p< 0.01). The SF concentration in the 18-44-y subgroup was lowest (p<0.01). The SF concentrations in the 6-11 and 45-59-y subgroups were significantly higher than those of 12-17 and 18-44-y subgroups (p<0.01).

As shown in Table 2 and Figure 4 for AWG, the sTfR concentrations in the 6-11 and ≥60-y subgroups were significantly lower than those of the other three subgroups (p<0.01), but there was no difference between the 6-11 and ≥60-y subgroup.

As shown in Table 2 and Figure 6 for AWG, the BI concentration in the ≥60-y subgroup was the highest (p<0.01). The BI concentration in the 18-44-y subgroup

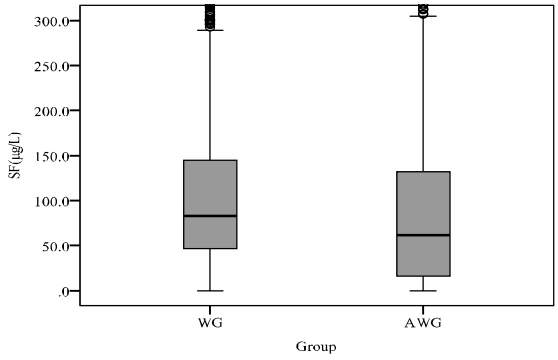

Figure 1. Box-plots presenting distribution of SF in WG and AWG.

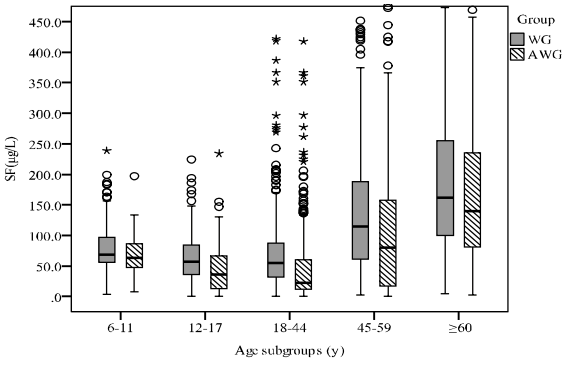

Figure 2. Box-plots presenting distribution of SF according to age in WG and AWG.

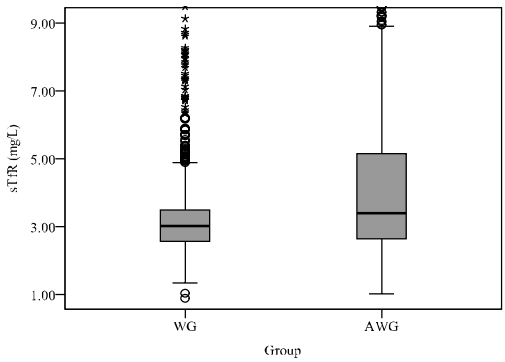

Figure 3. Box-plots presenting distribution of sTfR in WG and AWG

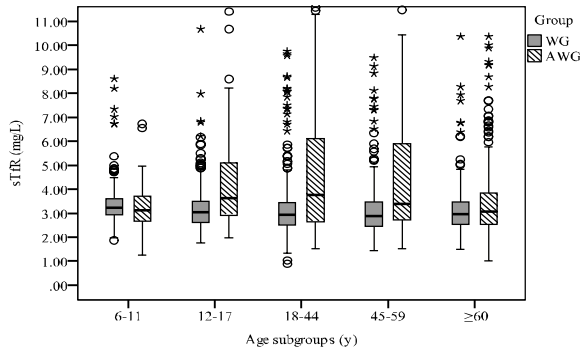

Figure 4. Box-plots presenting distribution of sTfR according to age in WG and AWG

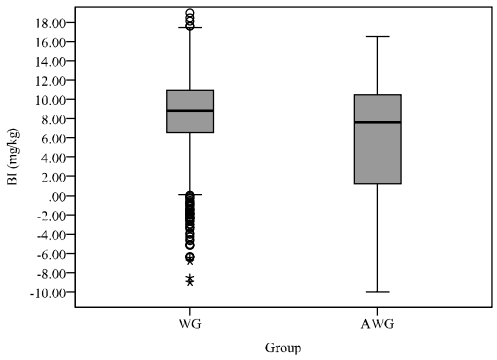

Figure 5. Box-plots presenting distribution of BI in WG and AWG

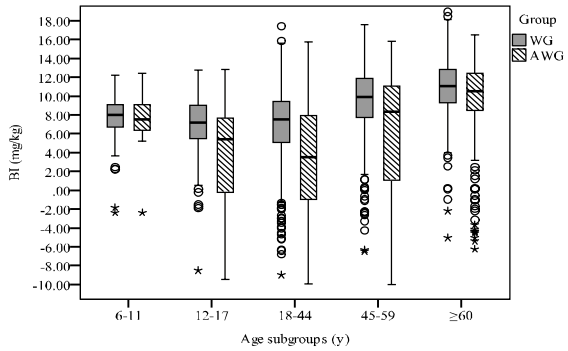

Figure 6. Box-plots presenting distribution of BI according to age in WG and AWG. The lower and upper edges of the box indicate the 25th and 75th percentiles, the horizontal line inside the box indicates the median and the whiskers indicate adistance of 1.5 × the interquartile range or the maximum and minimum values (whichever is smaller). Outliers are indicated with circles beyond the whiskers.

was lowest ($p<0.01$). The BI concentrations in the 6-11 and 45-59-y subgroups were significantly lower than that of the ≥60-y subgroup ($p<0.05$), but significantly higher than the other two subgroups ($p<0.01$).

In comparison to WG, the SF, sTfR and BI concentrati ons in the 12-17, 18-44, 45-59 and ≥60-y subgroups in AWG were significantly worse ($p<0.01$), but there was no difference for the SF, sTfR and BI concentration in the 6-11-y subgroup (Figure 1-6).

DISCUSSION

Iron status is considered the basic data for iron nutrition improvement since ID and IDA have been evidenced one of major cause of maternal and infant morbidity, mortality and impaired functional capacity.[13-15]

SF is widely used as a marker of iron storage. It is a quantitative measure of the size of body iron recommended as a suitable indicator by WHO.[16] However, SF is also an acute phase protein. It may not accurately reflect iron status in case of occurrences of infection, inflammation, and liver diseases.[17,18] The acute phase protein hsCRP was used to identify the participants with infection and inflammation, which could confound measures of SF.[19] About 5.9% and 1.6% of the samples had elevated hsCRP concentrations (>5 mg/L) in WG and AWG, respectively. The blood samples with hemolysis, clots or chylomicrons were excluded since the accuracy of measurement could be affected. The SF concentrations are commonly considered to be normally within the range 15-300 μg/L.[16,20] Cook et al measured the SF of 323 children aged 5-11 y and 125 women from low income families in Washington and found that the median values of SF concentration were both 21 μg/L.[21] Milman and Ibsen randomly selected 335 children aged 6-11 y and 305 women aged 12-17 y from urban locations in Denmark and found that the median values of SF concentration were 29 and 25 μg/L, respectively.[22] In our study, the median values of SF were 69.0 and 57.5 μg/L for the girls aged 6-11 y and 12-17 y in WG, respectively. The median values of SF were 62.8 and 36.0 μg/L for the girls aged 6-11 y and 12-17 y in AWG, respectively. Custer et al analyzed the distribution of SF according to age and sex for all participants and found that the 50th percentiles of the SF concentration for the subgroups of normal women aged less than 44 y group and higher than 44 y group were 24-39 and 37-81 μg/L, respectively.[23] Our study showed the same distribution tendency in both WG and AWG. The mean value of SF concentration was lowest in women aged 18-44 y, reflecting that women had lower iron stores caused by the losses during menstruation and childbirth.[24] The women after the menopause showed an increased SF concentration. Iron levels of adolescent girls were rather low and their ID risk should be relatively high because of their high iron requirements, especially during the growth spurt period. In addition, the onset of menstruation leads to iron losses.[25,26] It is also well known that adolescent girls have poor eating habits for gaining less weight.[27] In the HELENA Study, the mean SF value in girls aged 12.5-17.5 y was 27.9 μg/L, which was lower than that of adolescent girls in our study. The elderly women in this study had a significantly higher geometric mean SF than did the women of the other subgroups both in WG and AWG. In the elderly patients a high concentration of SF is often associated with some diseases.[28,29] Low SF values indicate ID but high values do not necessarily mean increased body iron stores. Inflammation, liver disease, hematologic malignant disease and haemolyticanemia may increase the SF concentration. Our study showed the highest SF concentration was in the ≥60-y subgroup among all the subgroups in the two groups and it may be related to impact from diseases partially. Similar to studies in the Australia,[30] the SF concentrations were higher in women in the postmenopausal age groups (50 y and above) than that in premenopausal age groups.

The sTfR concentration is less affected by inflammation than SF.[31] The sTfR concentrations were highest in the girls aged 6-11 y than those in both adolescent girls and adult women in WG, which was similar to the results from several researches.[32-34] In contrast, the sTfR concentration was the lowest in girls aged 6-11 y in AWG. One possible explanation is that IDA may not be the dominant type among different types of anaemia in the 6-11-y subgroup. Theoretically, the level of SF was negatively associated with level of sTfR and the measured data clearly consistent to the metabolism relationship of SF and sTfR.

BI is a newly suggested iron indicator measured by the ratio of sTfR to SF, proposed by Cook et al.[11] BI allows a full range evaluation of iron status from deficiency to excess and provides more information on iron status compared with other iron indexes since both SF and sTfR were included. Usually a negative BI is considered ID. In WG, the 5th percentile of BI in the 18-44-y subgroup was negative. However, in AWG, the 5th percentiles of BI of all the subgroups were negative, except the 6-11 and ≥60-y subgroups, and the 25th percentiles in the 12-17 and 18-44-y subgroups also negative. The elderly women aged ≥60-y subgroup had a higher mean of BI than that of the other subgroups. The women aged 18-44-y subgroup showed a lower mean of BI than those of the other subgroups. A pattern with the highest concentration in ≥60-y subgroup and the lowest concentration in 18-44-y subgroup for BI was consistent with that for SF. BI values were 6-7 mg/kg in the 6-11 and 12-17-y subgroups in WG. In the HELENA Study, a biochemical evaluation of iron status was performed with a cross sectional approach, and BI was 3.3 mg/kg in the girls aged 12.5-17.5 y.[25] No comparable data are available in the literature in relation to the distribution of SF, sTfR and BI of the girls and adult women in the Chinese in context of comparison with the results of the present study.

The results of the observation suggested that the iron status was worse in AWG than that in WG among all the observed groups, except 6-11-y subgroup. This finding was predictable, as iron deficiency is known to be a strong determinant of anaemia. A possible explanation for the higher SF and BI in 6-11-y subgroup in AWG could be explained that IDA might not be the major cause of the anaemia or low sample size due to low anaemia rate. Both in WG and AWG, the iron status of 18-44-y women was the lowest in terms of the SF, sTfR and BI. The iron status of the 12-17-y subgroup was also low.

The distribution of SF, sTfR and BI reflected characteristic of the observed groups in terms of iron nutrition status. SF and sTfR showed originally positively skewed

arrangement which could be transformed to normal distribution by logarithmic calculation.[35] BI showed normal arrangement that might be induced by the logarithmic equation. The arrangement of SF, sTfR and BI could be the reference database for the establishment of the cutoff for population groups.[16] In addition, the risk analysis of large population based intervention project of iron deficiency must rely on the distribution of these indicators.[7,16]

In conclusion, the observations here presented the distribution of SF, sTfR and BI for the whole community of girls and women in urban areas in China. The comparison of SF, sTfR and BI as indicators among age subgroups were also conducted in WG and AWG, respectively. The data supported the understanding of iron status in women and further analysis on ID should be needed. Evaluation of promotion project specifically targeted to women for ID and IDA could be reviewed with the data in this observation in China. Further observations are needed for other population groups, and it is recommended that a national monitoring system of iron status as well as other nutrients should be established.

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AUTHOR DISCLOSURES

Lijuan Wang, Jian Huang, Hong Li, Jing Sun, Jianhua Piao, Xiaoguang Yang, Guansheng Ma and Junsheng Huo, have no conflicts of interest.

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Original Article

Distribution of iron status among urban Chinese women

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中国大城市女性铁营养状况分布

背景与目的：评估不同年龄和贫血状况女孩和成年女性的血清铁蛋白、血清转铁蛋白受体和铁储量的分布情况。**方法与研究设计**：2010 年中国居民营养与健康状况监测中，对 1625 名普通女性和 1372 名贫血女性分别测定其血清铁蛋白、血清转铁蛋白受体和高敏 C 反应蛋白浓度。**结果**：6-11、12-17、18-44、45-59 和≥60 岁不同年龄组女性之间血清铁蛋白、血清转铁蛋白受体和铁储量的分布显著不同。在普通女性组和贫血女性组中，18-44 岁年龄组的女性铁营养状况均为最差，其次为 12-17 岁年龄组。在 12-17、18-44、45-59 和≥60 岁年龄组中，贫血女性的铁营养状况显著低于普通女性组。**结论**：不同年龄组及贫血状况女性的铁营养状况分布不同，贫血组女性的铁营养状况较普通女性组差。本研究观察到的中国大城市女性铁营养状况的数据，支持开展针对女性的铁营养改善的项目规划，也需要调查男性铁营养状况，并探究可能与铁摄入或损失的发病机制。

关键词：铁缺乏、贫血、血清铁蛋白、血清转铁蛋白受体、铁储量